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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/237,291	01/25/1999	JUDY CAROL YOUNG	SYS-2068	9391

1095 7590 10/08/2003

THOMAS HOXIE  
NOVARTIS, CORPORATE INTELLECTUAL PROPERTY  
ONE HEALTH PLAZA 430/2  
EAST HANOVER, NJ 07936-1080

EXAMINER

LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 10/08/2003

27

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/237,291

Applicant(s)

YOUNG ET AL.

Examiner

Karen A. Lacourciere

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 18-20, 23-27, 31-34, 37-43, 46, 47 and 52 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 18-20, 23-27, 31-34, 37-43, 46, 47, 52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 January 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 30, 2003 has been entered.

### ***Drawings***

In order to avoid abandonment, the drawing informalities noted in Paper No. 24, mailed on 12-31-2003, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper. As set forth in the letter accompanying the Draftsperson's drawing review, mailed with the Office action of 12-31-2003, and further set forth in MPEP 37 CFR 1.85(a), drawings will not be held in abeyance and if not corrected in the time period set forth in this Office action the application will be held ABANDONED.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-20, 23-27, 31-34, 37-43, and 46-50 are maintained as rejected and newly submitted claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387) or Davis et al. (US Patent 5,599,703), in view of Ku et al, Kobayashi et al, Ramsfjell et al (IDS Reference AK), Ohmizono et al, Szilvassy et al, Escary et al., or Bodine et al, and further in view of Tushinski et al (IDS Reference AN), Fletcher et al., Bello-Fernandez et al, or Hatzfeld et al. and Hanenburg et al. (Nature Medicine, Vol. 2, No.8) or Heneburg et al. (IDS reference AR) for the reasons of record set forth in the prior Office actions.

### ***Response to Arguments***

Applicant's arguments filed 06-30-2003 have been fully considered but they are not persuasive.

In response to the rejection of record under 35 USC 103(a) Applicant argues that none of the cited references provides both the requisite motivation and reasonable expectation of success without a loss of some or all of that pluripotent property.

Applicant argues that the reference Ku et al. does not teach TPO in combination with FL in the growth of CD34<sup>+</sup> hematopoietic cells because Ku et al. teaches use of sTPOR in combination with FL, however sTPOR is not an mpl ligand, as defined in the specification. Applicant argues that the sTPOR utilized by Ku et al. would actually counteract the effects of FL by binding any excess of mpl ligand and, therefore, teaches away from the claimed invention. This is not found to be persuasive because Ku et al. teach that TPO, an mpl ligand supports formation of multilineage colonies from marrow, that SF also stimulates colony formation and further, that the combination of TPO and SF stimulates colony formation (see for example, Table 1, page 4126). Additionally, Ku et al. indicates that SF stimulates even in the presence of sTPOR and TPO, and does not suppress colony formation, as Applicant argues (see for example, column 1, page 4126). Applicant equates the effects of sTPOR and SF or FL in cell lines and, given that SF effects appear independent of sTPOR in the presence of TPO, the skilled artisan likewise would not expect that the observed effects of sTPOR were the result of TPO binding for the effects observed with FL.

Applicant argues that Kobayashi et al. does not teach or suggest that FL or TPO or any other mpl ligand are useful in stimulating growth of pluripotent human hematopoietic stem cells without loss of pluripotency because it is not clear that the reference used a population of cells comprising a subpopulation of CD34<sup>+</sup>Thy-1<sup>+</sup>Lin<sup>-</sup> cells and further that the results demonstrate that the combination of SF, FL, and TPO supported formation of only a few colonies and that addition of IL-3 to that cytokine mix was required for a significant increase in colony formation. Applicant argues that

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Kobayashi et al. teach that this combination actually results in stimulation of the production of cells with a loss of pluripotency. Applicant argues that Kobayashi et al. teach against the claimed methods because it teaches that the combination of FI and TPO (optionally with SF) does not effectively support colony formation without the further addition of IL-3, wherein the addition of IL-3 is optional in the present invention. These arguments are not persuasive because the claimed methods are drawn to comprise addition of the particular cytokines and, therefore, encompass methods wherein IL-3 is additionally added. Further, it is very clear that methods wherein IL-3 is additionally added would be encompassed in the claimed methods, given that dependent claims are directed to methods wherein IL-3 is added as an additional step.

Applicant argues that Ohmizomo et al. demonstrates that the combinations of TPO, FL and IL-3 cause expansion of committed progenitors in a CD34<sup>+</sup> population of cells and that IL-3 is the pivotal cytokine. Applicant argues that IL-3 is not required in the instantly claimed methods and therefore, Ohmizomo et al. does not render the invention obvious. As discussed above, the claimed methods are open and would encompass methods wherein IL-3 is also administered to the cells. The claims are not directed to methods wherein TPO and FL are administered without IL-3.

Applicant argues that Ramsfjell et al. studied the effects of cytokines in multipotent human progenitor cells, however, that Ramsfjell et al. could not establish that TPO might expand the true long term reconstituting pluripotent stem cell. This is not persuasive because Ramsfjell et al. does demonstrate that multilineage cells are

provided with administration of the claimed combination of cytokines and multilineage cells would be encompassed in the term pluripotent.

Applicant argues that the conflicting results of Kobayashi et al. and Ohmizomo et al. combined with Ramsfjell et al.'s inability to demonstrate that TPO/KL/FL treatment did not destroy the lymphoid potential of the treated cells and doubts as to the true pluripotent nature of the cells treated with the combination highlight the uncertainty of the field and do not provide the guidance or expectation of success to the skilled artisan needed to render the claimed methods obvious. This is not persuasive because each of the references cited support that the claimed combination of cytokines does support the formation of multilineage colony formation and suggest to the skilled artisan that use of these cytokines would be successful in providing cells encompassed in the term pluripotent.

Applicant argues that the remaining references applied in the rejection of record do not make up for the deficiencies of Kobayashi et al. and Ohmizomo et al. and Ramsfjell et al. Applicant argues that although the cited references are used to teach the use of combinations of cytokines, these references do not teach the particular combination of cytokines wherein the cells maintain pluripotent properties.

Applicant additionally argues that their particular combination of cytokines, together with the inclusion of fibronectin is not obvious because the reference used to supply the fibronectin limitation, Hanenburg et al., does not teach or suggest any synergistic effect between fibronectin and the specifically claimed cytokines. Applicant argues that Example 9 and Figure 9 of the instant specification demonstrates

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synergistic effects between fibronectin and TPO and FL, whereas fibonectin in combination with other cytokines did not produce this synergistic effect. Applicant argues that these results provide a surprising and unexpected synergistic effect for FL and TPO and optionally other cytokines specified in the claims, and further, that expression is surprisingly enhanced in the hematopoietic cells in general, not just the pluripotent subpopulation. This is not found to be persuasive because Applicant is arguing unexpected results demonstrated with one particular cell line and one particular combination of cytokines encompassed within a broader scope of the claim. Applicant has not provided any evidence to suggest that this surprising and unexpected synergy would correlate to the full scope of the claimed methods.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere  
October 1, 2003

  
**KAREN A. LACOURCIERE, PH.D**  
**PRIMARY EXAMINER**